Addiction Medicine
and the Primary Care Physician

Drugs of Abuse—Opiates

WALTER LING, MD, *Los Angeles, and* DONALD R. WESSON, MD, *San Francisco*

Treating opiate-dependent patients can be difficult for many physicians because the patients' lifestyles, values, and beliefs differ from those of the physicians. Primary care physicians, however, are often involved in the treatment of the medical complications of opiate abuse, and physicians must often manage a patient's opiate dependence until appropriate referral to a drug abuse treatment program can be arranged. Treatment is guided by an understanding of the patient's addictive disease, for which there are specific diagnostic criteria, and an understanding of the pharmacology of opiates of abuse and the medications used in treating opiate dependence. The opiate agonist, methadone, is useful for both detoxification and maintenance. The opiate antagonist, naloxone, is the treatment of choice for opiate overdose, and naltrexone, also an opiate antagonist, is a useful adjunct in subgroups of opiate-dependent patients for preventing relapse. New medications for the treatment of opiate dependence are being developed.

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The term opiate originally was used to refer to drugs that were derived from opium. Now it is often used interchangeably with the term "opioid," a more general term that includes both the natural and synthetic drugs of this type, including the antagonists.

The term "narcotics," which implies a state of stupor, originally referred to drugs that produced morphinelike analgesia. The term causes much confusion because it is sometimes used by law enforcement agencies to refer to any potent, abusable drug. Although the term "narcotic" may seem obsolete because of its lack of precision, its use is likely to continue.

Both morphine and codeine are contained in opium. Other opioids, such as heroin, oxymorphone, or hydromorphone, are semisynthetics derived from ingredients of opium. Some other opioids, such as meperidine, methadone, levomethadyl acetate (levo-α-acetylmethadol), and fentanyl, are purely synthetics. There are also opiates known popularly as designer drugs, which are analogues of meperidine and fentanyl. (Several deaths resulted in the early 1980s from overdoses of α-methyl fentanyl, and, more recently, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine [MPTP], a neurotoxin from the synthesis of meperidine, caused acute parkinsonism in several abusers by destroying the dopamine-containing cells of the substantia nigra.) The term "designer drug," however, is not specific to opioids and may also refer to some nonopiates (such as methylenedioxymethamphetamine [MDMA]) manufactured in clandestine laboratories.

Clinical Pharmacology

Opioids exert their effects by binding with one or more of several specific types of opioid receptors. The extent and predominance of this binding between the substance and the specific receptors determines the pharmacologic profile. The degree to which the resultant manifestations resemble the physiologic and psychological effects of morphine can be used to classify these substances. Those resembling morphine effects are called opioid agonists and those producing no opioid effects are called antagonists. Those in between are mixed agonist-antagonists or partial agonists. Most opioids in clinical use for pain management are opioid agonists, and all are subject to abuse. Several mixed agonist-antagonists and partial agonists also are widely used for pain relief, but, unfortunately, they are also subject to abuse. There are currently two antagonists available for clinical use. Naloxone hydrochloride (Narcan) is used primarily to reverse the effects of opioids, and naltrexone is used to treat some subgroups of opioid addicts.

Opioid receptors were first discovered in the 1970s, and their discovery has greatly facilitated the understanding of opioid pharmacology. Today opioid receptors are understood as a general class with a number of subtypes, but the major clinical pharmacologic effects of opioids are related primarily to several major receptor types—mu (μ), kappa (κ), delta (δ), and sigma (σ). μ-Receptors have high binding affinity for morphinelike agonists. They mediate supraspinal analgesia, euphoria, physical dependence, respiratory depression, hypothermia, bradycardia, and miosis. Their activation suppresses the symptoms of opioid withdrawal. κ-Receptors, activated by butorphanol, nalbuphine, and pentazocine, mediate spinal analgesia, miosis, and sedation. Their activation does not invariably produce euphoria, but cessation after long-term administration does produce a withdrawal response as seen with μ-agonists. δ-Receptors also appear to mediate analgesia and appear to be the preferred site for endogenous opioid peptides. σ-Receptors may mediate the

From the Department of Psychiatry, University of California, Los Angeles, School of Medicine, and Los Angeles Drug Abuse Treatment Research Center (Dr Ling), and the Department of Psychiatry, University of California, San Francisco, School of Medicine, and Veterans Administration Medical Center, San Francisco (Dr Wesson).

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Reprint requests to Walter Ling, MD, 8447 Wilshire Blvd, Ste 409, Beverly Hills, CA 90211.

ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
FDA = Food and Drug Administration
HIV = human immunodeficiency virus
NIDA = National Institute on Drug Abuse

dysphoria produced by opioids and hallucinations, but its activation by the nonopioid phencyclidine raises questions of its being suitably classified as an opioid receptor.

Opioid receptors are widely distributed throughout the central nervous system. Those involved in pain and analgesia are in the locus ceruleus, the rapheal nuclei of the brain stem, the midbrain periaqueductal gray, and several hypothalamic and thalamic nuclei. Opioid receptors also appear in abundance in the dorsal horns of the spinal cord.

Central Nervous System Effects of Opioids

Although opioids have substantial effects on a number of body organ systems, those of interest in terms of their abuse relate principally to their effects on the central nervous system. These include analgesia, euphoria, sedation, and respiratory depression. With repeated use, tolerance and physical dependence develop.

Opioid-produced analgesia is unique in that both perception and reaction to pain are altered. Not only is the pain threshold raised, but the subjects become indifferent to the pain. This unique indifference to pain appears to involve higher cortical centers, most likely the frontal cortical areas, because the effects resemble those seen after prefrontal lobotomy.

Euphoria, an exaggerated state of well-being and freedom from anxiety and distress, is invariably described by long-term users of opioids. The euphoric effect is not always experienced with initial opiate use. Indeed, many addicts recall their first experience as being unpleasant, often accompanied by nausea and vomiting. With repeated use, however, the pleasurable, floating sensation predominates, and the addict begins to seek the experience. Drowsiness and some clouding of mentation often accompany opioid use, and sleep may be induced, although more often there is simply a feeling of tranquility and sleepiness without actual sleep.

Respiratory depression results from inhibition of the brain-stem respiratory center by opioids. The major respiratory effect results from a reduced responsiveness to carbon dioxide accumulation. The respiratory pattern becomes slow and shallow. This respiratory effect can be partially overcome by external stimuli, and street addicts frequently use painful stimuli to help their friends overcome the respiratory depressive effects in cases of overdose.

TABLE 1.—*Characteristics of Opiate Agonists*

Medication, Generic Name (Trade Name[s])	*Usual Single Dose for Pain, mg**	*Duration of Analgesia, h*	*How Abused*	*Abuse Liability*
Codeine	30-60	3-4 oral	Oral Injected	Low
Drocode (Synalgos-DC)	16-32	3-4	Oral	Moderate
Fentanyl citrate† (Sublimaze, Innovar‡)	0.05-0.1 IM	1-1.5	Injected	High
Fentanyl analogues, anesthetic use	...	...	Injected	High
Alfentanil HCl (Alfenta)				
Sufentanil citrate (Sufenta)				
Diacetylmorphine (heroin) HCl	...§		Snorted Injected	High
Heroin freebase			Smoked	
Hydrocodone bitartrate (Anexsia, Azdone, Damason-P, Hycodan, Vicodin)	5-10 oral	3-4	Oral	Moderate
Hydromorphone HCl (Dilaudid)	2-4 oral 1-2 IM	3-4	Oral, tablets dissolved and injected	High
Levomethadyl acetate [formerly L-α-acetylmethadol]	...	...	Oral	Moderate
Levorphanol tartrate (Levo-Dromoran)	2-3 oral 2-3 SC	4-8	...	High
Meperidine HCl (Demerol,¶ Mepergan#)	50-150 IM, or SC 100-200 oral	3-4	Injected	High
Methadone HCl	2.5-10 oral	3-5	Oral	High
(Dolophine**)	2.5-10 IM	3-5		
Morphine sulfate	10-15 IM	3-4	Injected	High
Opium	...	...	Smoked	Moderate
Oxycodone HCl (Percodan, Percocet)	5-10 oral	3-5	Oral Injected	Moderate
Oxymorphone HCl (Numorphan, injectable)	1-1.5 IM	4-6	Injected	High
Propoxyphene HCl (Darvon, Dolene, Wygesic)	32-64 oral	3-4	Oral	Moderate
Propoxyphene napsylate (Darvon-N)	50-100 oral	3-4	Oral	Moderate

HCl=hydrochloride, IM=intramuscularly, SC=subcutaneously

*Doses are for a nonopiate tolerant patient.
†Abused primarily by anesthesiologists. Fentanyl is sometimes available as a street drug of illicit manufacture known as "china white."
‡Fentanyl citrate in combination with droperidol, a sedating neuroleptic agent.
§Heroin has about 3 times the milligram potency of morphine.
‖Investigational medication for the treatment of opiate dependency.
¶Meperidine hydrochloride is available as a pharmaceutically manufactured tablet, but the tablet is not a common street drug of abuse. Injectable meperidine is, however, a common drug of abuse by nurses and other health professionals.
#Meperidine hydrochloride in combination with promethazine hydrochloride.
**Dolophine is the injectable form. It is not a common street drug of abuse.

TABLE 2.—*Characteristics of Mixed Opiate Agonist-Antagonists*

Medication, Generic Name (Trade Name[s])	*Usual Single Dose for Pain, mg*	*Duration of Analgesia, h*	*How Abused*	*Abuse Liability*
Buprenorphine hydrochloride* (Buprenex)	0.3-0.6 IM	6-8	Injected	Moderate
Butorphanol tartrate (Stadol)	1-4 IM	3-4	Injected	Moderate
	0.5-2 SC			
Nalbuphine hydrochloride (Nubain)	10 IM	3-6	Injected	Moderate
Pentazocine (Talwin Compound†)	20-30 IM	2-4	Oral	Low
(Talwin, injectable)	50 oral	3-5	Injected	Moderate
(Talwin Nx‡)			Injected	Low

IM=intramuscularly, SC=subcutaneously

*Buprenorphine hydrochloride is being studied as an opiate maintenance medication. Its use for this purpose is investigational.
†A combination of pentazocine hydrochloride and aspirin.
‡A combination of pentazocine and naloxone hydrochloride. The naloxone will prevent the opiate agonist effect if the capsule is dissolved and injected. Taken orally, the naloxone has no effect.

Suppression of the cough reflex and constricted pupils are also well-known effects of opioids. Many opioids are excellent cough suppressants, and miosis, to which little tolerance develops, is useful in diagnosing opioid intoxication even in long-term users.

In general, opioid effects are qualitatively similar as a group. They differ, however, with respect to potency, duration of action, and relative effectiveness after oral administration. Mixed agonist-antagonists are qualitatively distinct from agonists. Tables 1 and 2 depict, respectively, the characteristics of the better known agonists and agonist-antagonists.

Tolerance and Physical Dependence

At the cellular level, tolerance probably begins with the first dose of opioids, but it does not become clinically manifest until after repeated dosing of two to three weeks. Tolerance is best understood as the need for an increasing amount of the drug to achieve the same effect due to the progressive loss of effectiveness. The degree of tolerance depends on the interval between doses and the size of the dose: the larger the dose and the shorter the interval, the more pronounced the degree of tolerance. Tolerance, however, does not develop uniformly to all the pharmacologic effects of opioids. Notable tolerance develops quickly to analgesia, euphoria, sedation, and respiratory depression and only slightly and slowly to constipation and certain endocrine effects. It virtually does not develop to miosis. Nevertheless, tolerance is not complete to the euphoriant effect and to respiratory depression. For this reason, addicts continue to experience the desired sensation after each injection, and the danger of acute respiratory failure from overdose is ever present even in experienced addicts.

Cross-tolerance—the state in which a person tolerant to one opioid, such as morphine, is also tolerant to another similar opioid, such as methadone—develops with respect to the analgesic, euphoriant, sedative, and respiratory effects among opioids acting at the same receptor. Cross-tolerance does not appear to develop between opioids acting on different receptors. Tolerance to agonist-antagonist agents does not generally produce cross-tolerance with agonists, and tolerance does not develop to the antagonist effect of the mixed agonist-antagonist, nor to pure antagonists.

Physical dependence occurs concomitantly with the development of tolerance and is characterized by the appearance of a specific abstinence syndrome, with manifestations opposite to the acute effects of the drug. The mechanism of tolerance and physical dependence appears to be related to cellular adaptation, involving changes in the calcium flux or adenylate cyclase inhibition.

Clinical Approach to Patient Assessment

A certain nonjudgmental attitude is necessary to effectively evaluate an addicted patient clinically. This is not always easy for physicians whose training tends to expose them to the devastating medical complications of drug abuse and addiction. Moreover, addicts conjure up images of thieves and criminals, and it is not always easy to separate the role of medicine from that of the justice system.

Most addicted persons can understand and accept the consequences of their own behavior, but, like children, they are irrationally sensitive to punishment and rejection. They may accept incarceration while resenting any suggestion that they have done something wrong to deserve the punishment. Understanding an addict's distorted perception of reality as part of his or her illness helps prevent the physician from becoming frustrated and prevents the addict from perceiving or misperceiving rejection on the part of the physician.

Because of addicted persons' general difficulty with authorities, they come to physicians with a certain degree of mistrust and resent having to seek help in this context. It helps to minimize the authoritarian structure in the initial encounter. It is important to avoid any interruption or distraction during the interview. Physicians become vulnerable under the pressure of time and subject to addicted patients' manipulations. Simple language is preferred. It is better to avoid using street terms unless the physician is certain of the terms' meanings. Hearing street terms misused makes addicts feel "one up" and tends to encourage their manipulative behavior.

An addicted patient should be assured of the confidential nature of the conversation, but questioning should be direct and to the point. Addicts will give reliable enough histories, although some allowances must be made. For instance, they will admit to having been in jail while explaining that they went to jail to protect a friend or that the judge made an error. They will rationalize but usually will not deny facts when questioned directly. They are not likely to volunteer any such information, however, and a systematic approach to history taking is necessary.

The drug abuse history should include information about the age of first use; periods of heavy use, periods of abstinence, and the surrounding life circumstances; the pattern of current use, including frequency, amount, and time of last

TABLE 3.—*Medical Syndromes in Opiate Abusers**

Syndrome (Onset and Duration)	*Characteristics*
Opiate intoxication	Conscious, sedated, "nodding"; mood normal to euphoric; pinpoint pupils; history of recent opiate use
Acute overdose	Unconscious; pinpoint pupils; slow, shallow respirations
Opiate withdrawal	
Anticipatory† (3-4 hours after last "fix")	Fear of withdrawal; anxiety; drug craving; drug-seeking behavior
Early (8-10 hours after last "fix")	Anxiety; restlessness; yawning; nausea; sweating; nasal stuffiness, rhinorrhea; lacrimation; dilated pupils; stomach cramps; drug-seeking behavior
Fully developed (1-3 days after last "fix")	Severe anxiety; tremor; restlessness; piloerection‡; vomiting, diarrhea; muscle spasm§; muscle pain; increased BP; tachycardia; fever, chills; impulse-driven drug-seeking behavior
Protracted abstinence (may last up to 6 months)	Hypotension; bradycardia; insomnia; loss of energy, appetite; stimulus-driven opiate cravings

BP=blood pressure

*The times given in the table refer to heroin. Withdrawal will develop slower with long-acting opiates such as methadone.
†Anticipatory symptoms begin as the acute effects of heroin begin to subside.
‡The piloerection has given rise to the term "cold turkey."
§The sudden muscle spasms in the legs have given rise to the term "kicking the habit."

use; previous treatments, voluntary or involuntary; any complications relating to health, job, family, or conflict with the law; and the concomitant use of other drugs and the pattern of their use. It is useful to ascertain what brings the patient into contact with the physician at this particular time. This information provides some useful insight into true motivation and helps the physician to formulate realistic treatment goals.

Addicts tend to exaggerate their drug use but to minimize their other life problems. The history, therefore, should be supplemented by careful observation and physical examination. Common physical findings include fresh needle marks and old scars; thrombosed veins; abscesses; swollen nasal mucosa; enlarged liver and lymph nodes; and signs of intoxication or withdrawal, depending on the time of the last "fix."

Virtually all opiate addicts have abnormal liver function. This should improve with treatment unless other complications, such as alcohol abuse, supervene. All patients should be encouraged to obtain testing for the human immunodeficiency virus (HIV) and appropriate counseling regarding the acquired immunodeficiency syndrome (AIDS). Other sexually transmitted diseases, also common among addicts, need attention as well.

A urine drug panel is useful to detect opioids, metabolites, and other drugs of abuse. The presence of morphine indicates recent use but is not diagnostic of physical dependence, which requires the presence of a specific abstinence syndrome.

Abstinence can be precipitated with the narcotic antagonist naloxone, but this has only limited clinical usefulness because its results are influenced by many, largely uncontrolled, variables. Among them are the regular doses of opioids, duration, size, the frequency of use, the timing and size of the last dose of opioid, the dose of naloxone, and the expectation of the patient. Without adequate control of these variables, the degree of physical dependence cannot be accurately determined, especially when it is most needed, as in cases of mild dependence. Most clinicians no longer rely on naloxone challenge as a diagnostic tool. A negative naloxone challenge test, however, remains a useful prerequisite to naltrexone induction.

Clinical Diagnoses

A useful diagnostic distinction can be made between the maladaptive behavior associated with the regular use of opiates and the direct effects of the opiates on the central nervous system. The former consists of opioid dependence and opioid abuse. The latter includes the medical syndromes of opioid intoxication and opioid withdrawal. Acute overdose, a medical emergency, is a complication of acute intoxication. Table 3 summarizes some of the more common clinical features of opioid intoxication, acute overdose, and opioid withdrawal.

The American Psychiatric Association's diagnostic criteria now consider the central features of opioid dependence as a cluster of cognitive, behavioral, and physiologic symptoms that indicate impaired control over drug use and continued use despite adverse consequences.[1]

The presence of tolerance and withdrawal alone does not suffice for the diagnosis. Nine characteristic symptoms, with a time element, constitute the diagnostic criteria. A minimum of three symptoms must be present for a definite diagnosis. A set of criteria for rating the severity of the disorder is also provided.

Diagnostic Criteria for Opioid Dependence

At least three of the following must be present:

- Opioids are taken in larger amounts or over a longer period than the person intended;
- A desire for the drug persists, or the patient has made one or more unsuccessful efforts to cut down or to control opioid use;
- A great deal of time is spent in activities necessary to obtain opioids (such as theft), taking the drug, or recovering from its effects;
- The patient is frequently intoxicated or has withdrawal symptoms when expected to fulfill major role obligations at work, school, or home (for example, does not go to work, goes to school or work "high," is intoxicated while taking care of his or her children) or when opioid use is physically hazardous (such as driving under the influence);
- Important social, occupational, or recreational activities are given up or reduced;
- Continues opioid use despite the knowledge of having a persistent or recurrent social, psychological, or physical problem that is caused or exacerbated by the use of opioids (for instance, keeps using heroin despite family arguments about it);
- Marked tolerance: needs greatly increased amounts of the drug—at least a 50% increase—to achieve the desired effect, or a notably diminished effect occurs with continued use of the same amount;

• Has characteristic withdrawal symptoms (see opioid withdrawal syndromes in Table 3);
• Opioids are often taken to relieve or avoid withdrawal symptoms.

In addition, some symptoms of the disturbance have persisted for at least a month or have occurred repeatedly over a longer period to time.

Criteria for Severity of Opioid Dependence

The following criteria are used to determine the severity of opioid dependence:

Mild. Few, if any, symptoms are present in excess of those required to make the diagnosis, and the symptoms result in no more than mild impairment in occupational functioning or in usual social activities or relationships with others.

Moderate. Functional impairment or symptoms are between "mild" and "severe."

Severe. Many symptoms are present in excess of those required to make the diagnosis, and the symptoms greatly interfere with occupational functioning or usual social activities or relationships with others.

In partial remission. During the past six months, there has been some use of the substance and some symptoms of dependence.

In full remission. During the past six months, either there has been no use of opioids, or opioids have been used and there were no symptoms of dependence.

Opioid Abuse

Opioid abuse is now considered a residual category of the maladaptive pattern of opioid use that does not meet the diagnostic criteria of opioid dependence. The central feature is a continued use of the drug despite persistent and recurrent social, occupational, psychological, or physical problems caused by the use of the drug. A time element is also included.

Diagnostic Criteria for Opioid Abuse

A maladaptive pattern of opioid use is indicated by at least one of the following:

• There is continued use despite a knowledge of having a persistent or recurrent social, occupational, psychological, or physical problem that is caused or exacerbated by the use of opioids;
• There is recurrent use in situations in which opioid use is physically hazardous (such as driving while under the influence of opioids).

Other criteria are that some symptoms of the disturbance have persisted for at least a month or have occurred repeatedly over a longer period of time, or the patient clearly takes opiates but never met the criteria for opioid dependence.

Treatment of Opioid-Induced Medical Syndromes

Opioid Intoxication

Unless medical complications supervene, addicts do not seek treatment for their intoxicated state. The syndrome is not uncommonly seen at drug treatment clinics, however, and clinical observation is prudent, although no specific intervention is required. The presence of intoxicated addicts in the clinic vicinity should alert a physician to the possibility of drug diversion.

Acute Overdose

Coma, pinpoint pupils, and slow—four to five per minute—shallow respirations are the classic triad of acute opioid overdose. The response to the intravenous administration of naloxone hydrochloride (0.4 to 0.8 mg) is diagnostic. A comatose patient regains full consciousness within seconds of the naloxone injection and frequently shows some signs of opiate withdrawal. This clinical characteristic is so specific that anything less dramatic suggests mixed-drug overdose or other causes of coma. Signs of precipitated opiate withdrawal, when present, usually pass quickly without a specific intervention. Slow injection will avoid the confusion and agitation that sometimes accompany too rapid a return to consciousness.

Naloxone is the treatment of choice for opioid overdose. It should be given intravenously and, after the initial dose, titrated according to the patient's clinical response. Naloxone is short-acting; its effects last from 15 to 20 minutes. The opioids causing coma, such as methadone, may be much longer-acting, and the patient may lapse back into coma as the antagonist effect diminishes. Patients should not be discharged after the initial response but should be observed at least several hours. If long-acting opioids such as methadone or levomethadyl acetate are involved, the patient should be admitted to a hospital.

Opioid Withdrawal and Detoxification

The severity of withdrawal symptoms is determined by the degree of physical dependence and environmental influences. Experiences from therapeutic communities suggest that most opiate addicts can undergo withdrawal in a supportive, structured environment without medications. The symptoms of withdrawal are likened to a bout of influenza under these circumstances.

Drug cravings can be intense during withdrawal and often will lead to relapse if drugs are available. Contrary to the belief of many addicts and some physicians, the craving occurs not because of the absence of drugs but, rather, because of their potential availability. When drugs are truly unavailable, cravings usually subside quickly.

At present, the two most commonly used medications for detoxification are methadone and clonidine. Methadone is widely used for outpatient detoxification in methadone treatment clinics. The underlying principle is simple and straightforward. A longer-acting opioid, methadone, given orally once daily, generally in doses as high as 30 mg, is substituted for the opioids of abuse: heroin, meperidine, codeine, and the like. The patient is stabilized for several days, and the methadone is then gradually withdrawn. Although federal regulation now allows methadone detoxification to extend as long as 180 days,[2] California and most other states restrict methadone detoxification to 21 days. With a 21-day methadone detoxification of persons with a long-term opioid addiction, only a few patients achieve opiate abstinence, and, for those who do, relapse is frequent.

Many opiate addicts use outpatient methadone detoxification to lower the level of their physical dependence. Clinicians view the treatment as a humane exercise and an opportunity to bring the addict into contact with the drug abuse treatment system, in the hope that the addict will eventually commit to long-term treatment.

Methadone is a schedule II narcotic subject to stringent Food and Drug Administration (FDA) control. Under the

law, physicians are not permitted to prescribe it for the treatment of opioid addiction except in the context of a specially licensed program or unless the patient has an acute, concurrent medical condition.

Clonidine, an α-adrenergic agonist that suppresses opiate withdrawal, is not a scheduled medication. Although not FDA-approved for treating opiate withdrawal, clonidine is now commonly prescribed by private physicians and drug treatment programs for opiate detoxification. It is not an opiate, does not produce euphoria, and is not subject to abuse. When used for short-term opiate detoxification, clonidine does not produce physical dependence and can be discontinued with ease.[3,4]

One recommended regimen is to begin with 0.2 mg of clonidine hydrochloride given orally every four to six hours on the first day. The dose is adjusted to between 0.8 and 1.2 mg per day in divided doses for the next seven to ten days and tapered off over two to three days. Drowsiness and dizziness, from postural hypotension, are common side effects. Patients should be warned not to drive or operate machinery should drowsiness occur. Dizziness from postural hypotension can be relieved by lying down. The blood pressure should be monitored, and clonidine is withheld if the blood pressure falls to 90/60 mm of mercury or below.

Clonidine appears to be most effective in patients with signs of withdrawal. It is helpful for patients to learn this firsthand by an appropriate timing of the initial dose. A transdermal clonidine patch is now available and can be used in combination with oral clonidine in the following manner: Patients showing objective signs of withdrawal are given 0.2 mg of oral clonidine sublingually and two or three #2 clonidine transdermal patches—two if the patient weighs less than 68 kg (150 lb), three if more than 68 kg. The sublingual dose is repeated in an hour if the signs of withdrawal persist. Otherwise patients receive 0.2 mg of clonidine orally every six hours for the next two days. The patches are left for seven days for heroin withdrawal and ten days for methadone withdrawal.[5,6]

Suppression of the withdrawal syndrome by clonidine is incomplete. Ancillary medications for pain (acetaminophen or ibuprofen) and sleep (chloral hydrate), used judiciously, are generally effective.

Recidivism is high among addicts with established physical dependence whether detoxification is accomplished with methadone, clonidine, or some other method. In view of the current AIDS epidemic and the high risk of HIV exposure from continued "street" drug use, it would appear that detoxification alone does not suffice but should be used as a transitional step towards a longer-term treatment plan, which may include treatment with methadone, levomethadyl, buprenorphine, or naltrexone.

Treatment of Opioid Dependence

Methadone Maintenance

Methadone, in use since the 1960s, is covered elsewhere in this issue of the journal.* It is the only opioid presently approved by the FDA for the long-term treatment of opioid dependence.

Levomethadyl Acetate

Levomethadyl acetate (formerly levo-α-acetylmethadol), first synthesized in the 1940s, is a congener of methadone. It has been extensively studied, and there is an ongoing effort by the National Institute on Drug Abuse (NIDA) to make it available for general clinical use. It is an effective analgesic with some unique characteristics: it has a delayed onset and a long duration of action, and, because of its biotransformation in the liver, it is relatively more effective after oral, rather than parenteral, administration.

Clinical interest in levomethadyl as an alternative to methadone prompted a series of clinical trials by individual investigators and three large-scale multiclinic studies. The results of these investigations suggest that levomethadyl is comparable to methadone in clinical safety and efficacy but has a number of advantages. Pharmacologically, levomethadyl itself is relatively inactive, and its slow onset of action after parenteral administration makes it less subject to abuse by street addicts seeking an instant "high." Its long duration of action allows for three-times-per-week clinic attendance without take-home medications, thus eliminating the street diversion of take-home doses. Fewer clinic visits increase a clinic's treatment capacity and reduce patients' feelings of dependence on the clinic. Because take-home privileges no longer are an issue, patients are less compelled to lie to staff to protect their take-home privileges, and a more open, honest atmosphere prevails at the clinics. Because of its slower onset and more sustained action, patients feel less sedated.

No significant adverse effects were noted in the three large clinical trials with more than 3,500 patients, some treated for a year and longer. Other studies also support the drug's clinical safety.[7,8]

Only a few women have been treated with levomethadyl.[9] More experience in treating women with this drug is needed in view of the increasing number of opiate-dependent women seeking treatment.

Because levomethadyl is an orphan drug, the responsibility for filing a new drug application falls on the NIDA. A submission to the FDA was made in September 1979, but little has happened in the ensuing years. Recently the NIDA has initiated new efforts to complete the new drug application process, and it is hoped that levomethadyl will become available for general clinical use soon.

Naltrexone

Naltrexone is related to naloxone (Narcan), the only other currently available pure narcotic antagonist. It is produced by substituting the *N*-allyl of naloxone with the cyclopropylmethyl radical of another antagonist, cyclazocine, thus combining the relatively pure antagonist action of the former and the long duration of action and oral effectiveness of the latter. Clinical trials in the 1970s and early 1980s indicate that naltrexone can be a useful adjunct in the treatment of opioid dependence.[10,11] It was approved by the FDA for general use in 1984 and is available under the trade name Trexan.

Naltrexone comes as close to being an ideal narcotic antagonist as can be hoped for. It is quickly absorbed after oral administration, reaching a peak plasma concentration within an hour, and begins to work even sooner. Its effects are long-lasting; a single oral dose of 50 mg blocks the euphorigenic effects of a 25-mg dose of heroin for as long as 24 hours, and 150 mg provides blockage for as long as 3 days. It does not produce euphoria or cause dysphoria. It is not addicting, has no street value, and addicts do not abuse it.

The clinical use of naltrexone, however, is not without problems. It cannot be administered to addicts for as long as

*J. E. Zweben, J. T. Payte, "Methadone Maintenance in the Treatment of Opioid Dependence—A Current Perspective," pp 588-599.

there is opioid in their systems. This means that for most addicts, naltrexone cannot be prescribed for them when they first seek treatment as most addicts come to treatment with a history of recent use. Detoxification using methadone, clonidine, or some other method is a prerequisite of naltrexone therapy for most addicts.

An opioid-free interval is necessary to avoid a precipitated withdrawal by the initial dose of naltrexone. An interval of 5 to 7 days is recommended for heroin and 10 to 14 days for methadone. The period can be shortened somewhat by giving repeated doses of naloxone. The technique is not altogether innocuous, and it is advisable for physicians to familiarize themselves with it first by working with an experienced physician.

The drug-free state should be verified by administering a naloxone challenge. One method is to place 0.8 mg of naloxone in a syringe and administer 0.2 mg of it intravenously followed by a 30-second observation period for any symptoms or signs of withdrawal. If none are observed, the remaining 0.6 mg is given and the patient observed for an additional 20 minutes, during which symptoms and signs of withdrawal and vital signs are serially recorded. A worksheet can be constructed for this purpose to allow some quantification of the results. If a patient shows even minor symptoms and signs of withdrawal, he or she will likely not tolerate the initial dose of naltrexone, and the procedure should be repeated 24 hours later. If a negative test results, the patient can be administered an initial dose of 25 mg (half a tablet) of naltrexone and observed for another hour. If all goes well, the other 25 mg (half a tablet) can be given, bringing the first daily dose to 50 mg. Thereafter, several dosage schedules are available: Naltrexone can be given 50 mg daily; 100 mg Monday and Wednesday, and 150 mg Friday; or 150 mg Monday and 200 mg Thursday.

Naltrexone is well tolerated and side effects are uncommon. The manufacturer of the medication, DuPont Pharmaceuticals, has prepared a product monograph summarizing the results of most major clinical trials. There are also educational materials for physicians and patients. These are useful and may be obtained from representatives of the manufacturer.

Once a naltrexone regimen is initiated, patients cease craving and using opiates. This relates to the complete blockage of the euphorigenic effect of opiates by naltrexone. It is as though the patients realize that drugs (drug effect in this case) are truly no longer available. It is good clinical strategy to teach patients the relationship between the availability of drugs and craving. When an addict's access to an opiate effect is made unavailable by naltrexone, opiate craving ceases.

While naltrexone's ability to block the effects of opiates is certain, its place in the long-term treatment of opioid addicts is limited by low patient acceptance and by the high failure rates of opiate detoxification—a necessary first step to naltrexone treatment. Certain subgroups of patients, physicians, and other professionals, for instance, and other people with a higher socioeconomic status do better with naltrexone than do "street" addicts.[12] The reasons are not always clear but probably relate to their having a great deal more to lose, so to speak, and having experienced successful drug-free lives before. Many physicians are able to practice while receiving naltrexone, and, for some, the drug has been lifesaving.

Many addicts, while well motivated, are unable to resist the urge to use drugs after detoxification long enough to allow naltrexone induction. Buprenorphine may offer new hope.

Buprenorphine Hydrochloride

Buprenorphine hydrochloride, a partial agonist analgesic with both agonist and antagonist effects, has been undergoing clinical investigation for the treatment of opioid dependence for more than a decade. A parenteral form of the drug (Buprenex) has been approved by the FDA for the relief of moderate to severe pain, but its use for the treatment of opioid dependence remains investigational.

Buprenorphine blocked the effects of morphine in early clinical trials with addicts. Naloxone administration did not precipitate acute withdrawal in patients treated with buprenorphine. Abrupt discontinuation after eight weeks of buprenorphine treatment resulted in only a mild morphine-like withdrawal, and, while taking buprenorphine, subjects stopped the self-administration of heroin.[13,14]

In another study, 2 mg of buprenorphine was given subcutaneously to eight subjects in place of their daily dose of methadone (mean daily dose of 36 mg). Only mild discomfort resulted, and after 28 days of buprenorphine administration, an abrupt placebo substitution resulted in a mild withdrawal syndrome of several days' duration.[15] In a double-blind short-term study, 2 mg of sublingual buprenorphine was found to be comparable to 30 mg of methadone.[16] Illicit opioid use in this study was common and suggests a need for a higher dosage.

More recently, in a 30-day outpatient open-label clinical trial, buprenorphine in doses of 2, 4, and 8 mg given sublingually was effective in maintaining abstinence and keeping patients in treatment. At the conclusion of the trial, the buprenorphine administration was abruptly discontinued. Patients maintained on the 8-mg dose had a substantial increase of withdrawal symptoms. Those on 2- and 4-mg doses had only minimal withdrawal, and 7 of the 16 patients were successfully started on a regimen of naltrexone.[17]

These clinical trials involved only a small number of patients, and they need to be confirmed with controlled studies of larger numbers. The results thus far, however, are promising and suggest that buprenorphine could be an effective agent for detoxification as well as maintenance. If further studies confirm that patients can be abruptly switched from buprenorphine to naltrexone, buprenorphine can become a useful transitional drug from street heroin and methadone to naltrexone.

There has been a great deal of excitement surrounding the recent observation that using buprenorphine may reduce cocaine use.[18,19] Because cocaine abuse is found in as many as 40% of methadone-treated opioid addicts, substituting buprenorphine may reduce cocaine abuse in this population. There is also some suggestion that antagonists may reduce alcohol consumption. It would be of interest to know if buprenorphine, a partial agonist, will also reduce drinking, a major problem among methadone-maintenance patients because an opiate antagonist cannot be used with these patients.

Buprenorphine is not entirely free of abuse liabilities, although it may be less addictive than methadone. Some buprenorphine abuse by addicts has been reported in Europe and Australia where the drug is available in a tablet form.[20,21]

Therapeutic Community

Therapeutic communities for opioid addicts began in 1958 with the founding by Charles Diderich of the Synanon Foundation in Santa Monica, California. Today's therapeutic communities are highly structured residential treatment facilities. While treatment philosophy may differ from one therapeutic community to another, virtually all stress a complete abstinence from all drugs and strictly prohibit physical violence. Most therapeutic communities now embrace a 12-step recovery process similar to that of Alcoholics Anonymous, and most programs emphasize restructuring of lifestyles and resocialization through self-reliance, self-disclosure, peer pressure, and peer support. A detailed description of their philosophies, target population, and treatment approaches is beyond the scope of this article. A good general summary has been published by De Leon and Rosenthal.[22]

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